PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To: Karoline A. Delaney
Knobbe Martens Olson & Bear, LLP
2040 Main Street
Fourteenth Floor
Irvine, CA 92614

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference EKOS.165VPC	Date of mailing *(day/month/year)* 29 MAY 2007 **FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. PCT/US 06/13531	International filing date *(day/month/year)* 12 April 2006 (12.04.2006)
Applicant EKOS CORPORATION	

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/220 (January 2004) *(See notes on accompanying sheet)*

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference EKOS.165VPC	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 06/13531	International filing date *(day/month/year)* 12 April 2006 (12.04.2006)	(Earliest) Priority Date *(day/month/year)* 12 April 2005 (12.04.2005)
Applicant EKOS CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of _____ sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      ☒ the international application in the language in which it was filed
      ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,
   ☒ the text is approved as submitted by the applicant
   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   ☒ the text is approved as submitted by the applicant
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. 16
      ☒ as suggested by the applicant
      ☐ as selected by this Authority, because the applicant failed to suggest a figure
      ☐ as selected by this Authority, because this figure better characterizes the invention
   b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 06/13531

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) A61B 8/14 (2007.01); A61B 17/20 (2007.01)
USPC: 600/466;
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC: 600/466; 604/22

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 600/406, 467; 604/500, 509, 522, 22; 607/101, 105 (text search - see terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, USOC, EPAB, JPAB); Dialog PRO (Engineering); Google Scholar
Search Terms Used: Ultrasound, ultrasonic, catheter, cavitation, therapeutic, amplitude

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 2004/0024347 A1 (Wilson et al.) 05 February 2004 (05.02.2004), entire document especially para [0014]-[0018], [0102]-[0106] and [0095]	19, 21, 24, 25 --- 1-18, 20, 22, 23, 26-56
Y	US 6,508,816 B2 (Shadduck) 21 January 2003 (21.01.2003), entire document especially col 9, ln 26-32; col 10, ln 38-46	1-18, 22, 23, 30-35, 43-56
Y	US 5,342,292 A (Nita et al.) 30 August 1994 (30.08.1994), entire document especially col 4, ln 3-6; col 3, ln 26-35	2, 4, 20, 26-42, 44-46, 51-53
Y	US 6,524,251 B2 (Rabiner et al.) 25 February 2003 (25.02.2003), entire document especially col 4, ln 3-15; col 6, ln 32-36	41, 42, 45, 46, 52, 53

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2007 (03.04.2007)	29 MAY 2007
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2005)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: Karoline A. Delaney
Knobbe Martens Olson & Bear, LLP
2040 Main Street
Fourteenth Floor
Irvine, CA 92614

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	29 MAY 2007
Applicant's or agent's file reference EKOS.165VPC	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 06/13531	12 April 2006 (12.04.2006)	12 April 2005 (12.04.2005)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61B 8/14 (2007.01); A61B 17/20 (2007.01)
USPC - 600/466; 604/22

Applicant EKOS CORPORATION

1. This opinion contains indications relating to the following items:

- [X] Box No. I Basis of the opinion
- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [X] Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [ ] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	3 April 2007 (03.04.2007)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 06/13531

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____ , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 06/13531

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-18, 20, 22, 23, 26-56	YES
	Claims	19, 21, 24, 25	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-56	NO
Industrial applicability (IA)	Claims	1-56	YES
	Claims	None	NO

2. Citations and explanations:

Claims 19, 21, 24 and 25 lack novelty under PCT Article 33(2) as being anticipated by US 2004/0024347 A1 to Wilson et al. (hereinafter Wilson).

As per claim 19, Wilson discloses a method comprising positioning a catheter at a treatment site with a patients vasculature, the catheter being positioned partially within an occlusion (para [0106]); delivering a therapeutic compound from the catheter to the occlusion (para [0106]); and delivering a plurality of packets of ultrasonic energy from an ultrasound radiating member positioned within the catheter to the occlusion wherein the packets comprise a plurality of pulses of ultrasonic energy having an amplitude that varies pulse to pulse (para [0102]).

As per claims 21, 24 and 25, Wilson further discloses wherein the packets of energy are temporally separated by a period wherein substantially no energy is delivered to the site (para [0103]); measuring a temperature at the treatment site after at least one of the packets of energy is delivered to the occlusion (para [0095]); and modifying the amplitude of the pulses of energy in response to the temperature measurement (para [0095]).

Claims 1, 3, 5-18, 22, 23, 43, 47-50 and 54-56 lack an inventive step under PCT Article 33(3) as being obvious over Wilson in view of US 6,508,816 B2 (Shadduck).

As per claim 1, Wilson discloses a method of applying ultrasonic energy to a treatment site within a patients vasculature (para [0018]); comprising positioning an ultrasound radiating member at the site (para [0106]); and activating the member to produce pulses of ultrasonic energy at a cycle period T less than or equal to 1 (para [0102]-[0103]). Wilson does not disclose wherein each pulse of energy has a first peak amplitude for a first duration, and a second reduced amplitude that is less than the first amplitude for a second duration. Shadduck discloses wherein each pulse of energy has a first peak amplitude for a first duration, and a second reduced amplitude that is less than the first amplitude for a second duration (col 9, ln 26-32). It would have been obvious to one of ordinary skill in the art to modulate the amplitude of the energy pulses as taught by Shadduck in the method taught by Wilson in order to induce and maintain cavitation while avoiding heat damage to surrounding tissue.

As per claims 5, 6, 9 and 10, Wilson further discloses delivering a therapeutic compound to the treatment site concurrently with the ultrasonic energy (para [0014]); wherein the member operates with an acoustic efficiency greater than about 50% (para [0105]); wherein the pulses of energy have a duty cycle that is between about 1% and about 50%; and measuring a temperature at the site and adjusting the duty cycle based on the temperature measurement (para [0091]).

As per claims 3, 7, and 8, Wilson discloses a method of applying ultrasonic energy as discussed with respect to claim 1, above. Wilson does not disclose wherein at least a portion of the second duration occurs before the first duration is terminated; wherein the first peak amplitude induces cavitation at the site; and wherein the first duration is shorter than the second duration. Shadduck discloses wherein at least a portion of the second duration occurs before the first duration is terminated (col 9, ln 26-32); wherein the first peak amplitude induces cavitation at the site (col 10, ln 36-46); and wherein the first duration is shorter than the second duration (col 9, ln 26-32). It would have been obvious to one of ordinary skill in the art to control the duration and amplitude of the pulses as taught by Shadduck in the method taught by Wilson in order to induce and maintain cavitation while avoiding collateral damage to surrounding tissue.

As per claim 11, Wilson discloses a method comprising positioning an ultrasound radiating member at a treatment site within a patients vasculature (para [0106]); delivering pulses of ultrasonic energy to the treatment site from the member wherein the pulses include a variable amplitude (para [0102]-[0103]); and delivering a therapeutic compound to the site simultaneously with the delivery of the pulses (para [0014]). Wilson does not disclose wherein the pulses have an increased pulse amplitude during a first pulse segment and a reduced pulse amplitude during a second pulse segment. Shadduck discloses wherein the pulses have an increased pulse amplitude during a first pulse segment and a reduced pulse amplitude during a second pulse segment (col 9, ln 26-32). It would have been obvious to one of ordinary skill in the art to modulate the amplitude of the energy pulses as taught by Shadduck in the method taught by Wilson in order to induce and maintain cavitation while avoiding heat damage to surrounding tissue.

-----Please See Continuation Sheet----

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 06/13531

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box V.2. Citations and explanations:

As per claims 12, 13 and 15-18, Wilson further discloses wherein the first pulse segment occurs before the second pulse segment (para [0102]); the second pulse segment occurs before the first pulse segment (para [0102]); the pulses have a cycle period T less than or equal to one second (para [0102]-[0103]); and the sum of a duration of the first segment and a duration of the second segment is between about 5% and about 25% of the cycle period T (para [0103]). Wilson further discloses wherein a plurality of ultrasound radiating members are positioned at the site (para [0017]); a first ultrasonic waveform is delivered from a first ultrasound radiating member to the site; and a second ultrasonic waveform is delivered from a second ultrasound radiating member to the site (para [0014]); further wherein the first and second waveforms are delivered to the site simultaneously (para [0014]).

As per claim 14, Wilson discloses a method comprising positioning an ultrasound radiating member at a treatment site as discussed with respect to claim 11, above. Wilson does not disclose wherein the pulses have a pulse amplitude that varies linearly between the increased pulse amplitude and the reduced pulse amplitude. Shadduck discloses wherein the pulses have a pulse amplitude that varies linearly between the increased pulse amplitude and the reduced pulse amplitude (col 9, ln 26-32). It would have been obvious to one of ordinary skill in the art to vary the amplitude of the energy pulses as taught by Shadduck in the method taught by Wilson in order to induce and maintain cavitation while avoiding heat damage to surrounding tissue.

As per claims 22 and 23, Wilson discloses a method comprising positioning a catheter at a treatment site with a patients vasculature as discussed with respect to claim 19, above. Wilson does not disclose wherein the plurality of pulses of ultrasonic energy have an amplitude that varies sinusoidally from pulse to pulse; and the plurality of pulses of ultrasonic energy includes at least one trigger pulse having sufficient power to induce cavitation at the treatment site. Shadduck discloses wherein the plurality of pulses of ultrasonic energy have an amplitude that varies sinusoidally from pulse to pulse (col 9, ln 26-32); and the plurality of pulses of ultrasonic energy includes at least one trigger pulse having sufficient power to induce cavitation at the treatment site (col 10, ln 38-46). It would have been obvious to one of ordinary skill in the art to vary the amplitude of the pulses and to initiate cavitation with a pulse of sufficient energy to induce cavitation as taught by Shadduck in the method taught by Wilson in order to induce and control cavitation at the treatment site.

As per claims 43 and 47, Wilson discloses a catheter system comprising an elongate tubular body having a distal region and a proximal region opposite the distal region (para [0014]); an ultrasound radiating member positioned adjacent to the distal region of the tubular body (para [0014]); a fluid delivery lumen extending through at least a portion of the tubular body and a fluid delivery port that is configured to deliver a fluid within the fluid delivery lumen to a region exterior to the tubular body (para [0014]); and a control system configured to provide a control signal to the ultrasound radiating member wherein the signal causes the member to generate a plurality of pulses of ultrasonic energy (para [0017]). Wilson does not disclose wherein a first pulse of energy has an amplitude that is greater than a second pulse of energy; and wherein the plurality of pulses of energy have an amplitude that varies sinusoidally from pulse to pulse. Shadduck discloses wherein a first pulse of energy has an amplitude that is greater than a second pulse of energy (col 9, ln 26-32).; and wherein the plurality of pulses of energy have an amplitude that varies sinusoidally from pulse to pulse (col 9, ln 26-32). It would have been obvious to one of ordinary skill in the art to vary the amplitude of the pulses as taught by Shadduck in the method taught by Wilson in order to induce and control cavitation at the treatment site.

As per claims 48, 49, 55 and 56, Wilson further discloses wherein the first pulse of energy has a peak power of greater than about 15 watts (para [0067]); and the catheter system further comprises a temperature sensor wherein the control system is configured to modify the control signal based on a temperature signal generated by the temperature sensor (para [0095]).

As per claims 50 and 54, Wilson discloses a catheter system comprising an elongate tubular body having a distal region and a proximal region opposite the distal region (para [0014]); an ultrasound radiating member positioned adjacent to the distal region of the tubular body (para [0014]); a fluid delivery lumen extending through at least a portion of the tubular body and a fluid delivery port that is configured to deliver a fluid within the fluid delivery lumen to a region exterior to the tubular body (para [0014]); and a control system configured to provide a control signal to the ultrasound radiating member wherein the signal causes the member to generate a plurality of pulses of ultrasonic energy (para [0017]); at a cycle period T less than or equal to one second (para [0102]-[0103]). Wilson does not disclose wherein a selected pulse of ultrasonic energy has a first peak amplitude for a first duration and a second reduced amplitude that is less than the first peak for a second duration; and wherein at least a portion of the second duration occurs before the first duration is terminated. Shadduck discloses wherein a selected pulse of ultrasonic energy has a first peak amplitude for a first duration and a second reduced amplitude that is less than the first peak for a second duration (col 9, ln 26-32); and wherein at least a portion of the second duration occurs before the first duration is terminated (col 9, ln 26-32). It would have been obvious to one of ordinary skill in the art to vary the power and amplitude of the pulses as taught by Shadduck in the catheter taught by Wilson in order to induce and control cavitation at the treatment site to effectuate ablation while minimizing collateral tissue damage.

Claims 20, 26-29 and 36-40 lack an inventive step under PCT Article 33(3) as being obvious over Wilson in view of US 5,342,292 A1 to Nita et al. (hereinafter Nita).

As per claims 20 and 26, Wilson discloses a method comprising positioning a catheter at a treatment site with a patients vasculature as discussed with respect to claim 19, above. Wilson does not disclose wherein the catheter includes a cavitation promoting surface that is exposed to the packets of ultrasonic energy; and wherein the ultrasound radiating member is movable with respect to the catheter. Nita discloses wherein the catheter includes a cavitation promoting surface that is exposed to the packets of ultrasonic energy (col 4, ln 3-6); and wherein the ultrasound radiating member is movable with respect to the catheter (col 3, ln 26-35). It would have been obvious to one of ordinary skill in the art to include a cavitation promoting surface and to allow the member to move relative to the catheter as taught by Nita in the method taught by Wilson in order to induce cavitation at lower energies and to direct the energy to selected treatment sites.

-----Please See Continuation Sheet-----

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 06/13531

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box V.2. Citations and explanations:

As per claims 27 and 28, Wilson discloses an ultrasound catheter configured to be inserted into a patients vascular system comprising an elongate outer sheath defining a central lumen that extends longitudinally from an outer sheath proximal region to an outer sheath distal region (para [0014]); an elongate hollow inner core positioned in the central lumen, the inner core defining a utility lumen (para [0014]); and an ultrasound radiating member having a hollow inner passage through which the inner core passes wherein the member is positioned generally between the inner core and outer sheath (para [0060]). Wilson does not disclose wherein the outer sheath includes an outer surface having a cavitation promoting region located adjacent to the ultrasound radiating member and a smooth region located proximal to the cavitation promotion region wherein the cavitation promotion region has an increased surface roughness compared to the smooth region; and wherein the outer sheath has an outer diameter of less than about 5.2 French. Nita discloses wherein the outer sheath includes an outer surface having a cavitation promoting region located adjacent to the ultrasound radiating member and a smooth region located proximal to the cavitation promotion region wherein the cavitation promotion region has an increased surface roughness compared to the smooth region (col 4, ln 3-6). It would have been obvious to one of ordinary skill in the art to include the cavitation promoting surface taught by Nita in the catheter taught by Wilson in order to induce cavitation at lower energies. Furthermore, it would have been obvious based upon experimentation and design choice to select 5.2 French as the size for the catheter in Wilson in order to utilize the catheter at the selected treatment site.

As per claim 29, Wilson discloses a catheter system for delivering ultrasonic energy and a therapeutic compound to a treatment site within a body lumen comprising a tubular body having a proximal end, a distal end and a fluid delivery lumen extending at least partially through the tubular body and having at least one outlet in an energy delivery section (para [0014]); an inner core configured for insertion into the tubular body, the inner core comprising a plurality of ultrasound radiating members connected to an elongate electrical conductor (para [0060]); and wiring such that a voltage can be applied from the elongate electrical conductor across a selected plurality of the ultrasound radiating members such that the selected pluralist of members can be driven simultaneously (para [0014]). Wilson does not disclose wherein the energy delivery section is positioned between the proximal end and the distal end wherein the energy delivery section includes a cavitation promoting surface having and increased surface roughness. Nita discloses wherein the energy delivery section is positioned between the proximal end and the distal end wherein the energy delivery section includes a cavitation promoting surface having and increased surface roughness (col 4, ln 3-6). It would have been obvious to one of ordinary skill in the art to include the cavitation promoting surface taught by Nita in the catheter taught by Wilson in order to induce cavitation at lower energies.

As per claims 36-40, Wilson discloses an ultrasound catheter comprising an elongate tubular body having a proximal region and a distal region wherein an energy delivery section is included within the distal region of the tubular body (para [0014]); an ultrasound radiating member positioned adjacent to the energy delivery section of the tubular body (para [0014]); a fluid delivery lumen positioned within the tubular body and a fluid delivery port that is configured to deliver a fluid within the delivery lumen to an exterior region of the ultrasound catheter (para [0014]); further wherein the fluid delivery lumen passes through a hollow inner core of the member (para [0014]); and the fluid delivery port is positioned at a distal end of the tubular body and on the exterior surface of the ultrasound catheter (para [0014]). Wilson does not disclose wherein the catheter comprises a cavitation promoting surface that is formed on an exterior surface of the catheter and that is exposed to ultrasonic energy when the member is activated; and wherein the fluid delivery port is positioned on the cavitation promoting surface. Nita discloses wherein the catheter comprises a cavitation promoting surface that is formed on an exterior surface of the catheter and that is exposed to ultrasonic energy when the member is activated (col 4, ln 3-6); and wherein the fluid delivery port is positioned on the cavitation promoting surface (col 6, ln 40-46). It would have been obvious to one of ordinary skill in the art to include a fluid delivery port positioned on the cavitation promoting surface taught by Nita in the catheter taught by Wilson in order to deliver therapeutic compounds to the cavitation area.

Claims 2, 4, 30-35, 44 and 51 lack an inventive step under PCT Article 33(3) as being obvious over Wilson in view of Shadduck, further in view of Nita.

As per claims 2 and 4, Wilson and Shadduck disclose the method of applying ultrasonic energy to a treatment site discussed with respect to claim 1, above. Wilson and Shadduck do not disclose wherein the method further comprises positioning a cavitation promoting surface at the treatment site such that the cavitation surface is present at the treatment site when the ultrasound member is activated; and wherein the ultrasound member is movable with respect to a catheter sheath that is positioned at the treatment site. Nita discloses positioning a cavitation promoting surface at the treatment site such that the cavitation surface is present at the treatment site when the ultrasound member is activated (col 4, ln 3-6); and wherein the ultrasound member is movable with respect to a catheter sheath that is positioned at the treatment site (col 3, ln 26-35). It would have been obvious to one of ordinary skill in the art to include a cavitation promoting surface and to allow the member to move relative to the catheter as taught by Nita in the method taught by Wilson and Shadduck in order to induce cavitation at lower energies and to direct the energy to selected treatment sites.

-----Please See Continuation Sheet-----

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 06/13531

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.
Continuation of:
Box V.2. Citations and explanations:

As per claims 30-35, Wilson discloses a method of treating a vascular occlusion comprising delivering a catheter with a plurality of ultrasound radiating members to a treatment site within a patients vasculature (para [0014]); wherein the occlusion is located at the treatment site (para [0106]); the ultrasonic energy has a duty cycle between about 1% and about 10% (para [0102]); and the ultrasonic energy has a frequency between about 1.2 MHz and about 2.2MHz (para [0067]). Wilson does not disclose wherein the method further comprises delivering an ultrasound contrast agent to the site. However, it would have been obvious, based upon experimentation and design choice, to one of ordinary skill in the art to include a contrast agent in the method taught by Wilson in order to visualize the treatment site.

Wilson also does not disclose wherein the catheter includes a cavitation promoting surface region having an increased surface roughness as compared to surface regions adjacent the cavitation promoting surface. Nita discloses wherein the catheter includes a cavitation promoting surface region having an increased surface roughness as compared to surface regions adjacent the cavitation promoting surface (col 4, ln 3-6). It would have been obvious to one of ordinary skill in the art to include the cavitation promoting surface taught by Nita in the method taught by Wilson in order to induce cavitation at lower energies.

Wilson also fails to disclose delivering ultrasonic energy to the site from the catheter so as to generate cavitation at the site; and wherein the ultrasonic energy has a peak acoustic pressure that is preferably between about 1.8 MPa and 3.8 MPa; and wherein the ultrasonic energy has a spatial average acoustic pressure that is preferably between about 1.4 MPa and 3.4 MPa. Shadduck discloses delivering ultrasonic energy to the site from the catheter so as to generate cavitation at the site (col 10, ln 36-46); and wherein the ultrasonic energy has a peak acoustic pressure that is preferably between about 1.8 MPa and 3.8 MPa; and wherein the ultrasonic energy has a spatial average acoustic pressure that is preferably between about 1.4 MPa and 3.4 MPa (col 10, ln 36-46). It would have been obvious to one of ordinary skill in the art to include inducing cavitation at the treatment site and to use suitable levels of acoustic pressure as taught by Shadduck in the method taught by Wilson and Nita in order to effectively ablate the occlusion without damaging surrounding tissue.

With respect to claims 44 and 51, Wilson and Shadduck disclose the catheter system discussed with respect to claims 43 and 50, above. Wilson and Shadduck do not disclose wherein the catheter system further comprises a cavitation promoting surface that is exposed to ultrasonic energy when the control signal is provided to the ultrasonic member. Nita discloses wherein the catheter system further comprises a cavitation promoting surface that is exposed to ultrasonic energy when the control signal is provided to the ultrasonic member (col 4, ln 3-6). It would have been obvious to one of ordinary skill in the art to include a cavitation promoting surface which is controllably exposed to ultrasonic energy as taught by Nita in the system taught by Wilson and Shadduck in order to induce cavitation at lower energies at selected treatment sites.

Claims 41 and 42 lack an inventive step under PCT Article 33(3) as being obvious over Wilson in view of Nita, further in view of US 6,524,251 B2 to Rabiner et al. (hereinafter Rabiner). Wilson and Nita disclose the ultrasound catheter discussed with respect to claim 36, above. Wilson and Nita do not disclose wherein when the ultrasound radiating member is activated, cavitation occurs adjacent to the cavitation promoting surface but does not occur adjacent to other regions; and wherein the cavitation promoting surface is configured to entrap gas pockets thereon when immersed in a liquid. Rabiner discloses wherein when the ultrasound radiating member is activated, cavitation occurs adjacent to the cavitation promoting surface but does not occur adjacent to other regions (col 4, ln 3-15); and wherein the cavitation promoting surface is configured to entrap gas pockets thereon when immersed in a liquid (col 6, ln 32-36). It would have been obvious to one of ordinary skill in the art to limit cavitation to the area around the cavitation promoting surface and to configure the cavitation promotion surface to entrap gas as taught by Rabiner in the catheter taught by Wilson and Nita in order to direct cavitation to selected treatment sites and to encourage cavitation at lower energies.

Claims 45, 46, 52 and 53 lack an inventive step under PCT Article 33(3) as being obvious over Wilson in view of Shadduck, further in view of Nita, further in view of Rabiner. Wilson, Shadduck and Nita disclose the catheter system discussed with respect to claims 44 and 51, above. Wilson, Shadduck and Nita do not disclose wherein the control signal is configured to cause cavitation in a region adjacent to the cavitation promoting surface but to not cause cavitation adjacent to other regions of the catheters; and wherein the cavitation promoting surface is configured to entrap gas pockets thereon when immersed in a liquid. Rabiner discloses wherein the control signal is configured to cause cavitation in a region adjacent to the cavitation promoting surface but to not cause cavitation adjacent to other regions of the catheters (col 4, ln 3-15); and wherein the cavitation promoting surface is configured to entrap gas pockets thereon when immersed in a liquid (col 6, ln 32-36). It would have been obvious to one of ordinary skill in the art to limit cavitation to the area around the cavitation promoting surface and to configure the cavitation promotion surface to entrap gas as taught by Rabiner in the catheter taught by Wilson, Shadduck and Nita in order to direct cavitation to selected treatment sites and to encourage cavitation at lower energies.

Claims 1-56 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article," "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application (claims, description and drawings) may be amended during the that, since all parts of the international application international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended ?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When ? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments ?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How ? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments ?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;
(ii) the claim is cancelled;
(iii) the claim is new;
(iv) the claim replaces one or more claims as filed;
(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers, claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority a reply to the written opinion together, applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.